PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 354. P2F	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/030743	International filing date *(day/month/year)* 17.09.2004	Priority date *(day/month/year)* 19.09.2003

International Patent Classification (IPC) or national classification and IPC
C07D471/04, C07D513/04, A61K31/4985, A61K31/437, A61K31/4375, A61K31/4365, A61K31/53, A61K31/519, A61P31/18, C07F9/02

Applicant
GILEAD SCIENCES, INC. et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13.04.2005	10.08.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fazzi, R Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/030743

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-153 as originally filed

   Claims, Numbers

   1-65 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 64-65

because:

☒ the said international application, or the said claims Nos. 64-65 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-65
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-65
Industrial applicability (IA)	Yes:	Claims	1-63
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1) Reference is made to the following documents:

D1: WO 2004/035576 A2
D2: WO 03/077850 A2
D3: WO 03/016315 A1
D4: WO 02/055079 A2
D5: WO 02/30426 A1
D6: WO 91/19721 A1
D7: KHAMNEI S. ET AL.: "Neighboring Group Catalysis in the Design of Nucleotide Prodrugs" J. MED. CHEM., vol. 39, 1996, pages 4109-4115, XP002315516
D8: LOMBAERT S DE ET AL: "N-Phosphonomethyl Dipeptides and Their Phosphonate Prodrugs, a New Generation of Neutral Endopeptidase (NEP, EC 3.4.24.11) Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, no. 4, 18 February 1994 (1994-02-18), pages 498-511, XP000564486 ISSN: 0022-2623

1.1) In view of their priorities dated, respectively, 29/04/2004 and 25/09/2003, the contents of documents D1 and D2 will not be used in this Written Opinion, but they could become relevant under Articles 54 and 56 EPC after the entrance into the European Phase.

2) Reference to section III

Claims 64-65 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

3) Novelty (Reference to section V)

D3-D5 describe compounds which are structurally close to those of present claims 1 and 30. However, they do not comprise any phosphonate groups.

D6-D8 disclose phosphorous prodrugs, which do not include any aza-quinolinol group.

Accordingly, the subject-matter of present claims 1-65 meets the requirements of Article 33(2) PCT.

4) Inventive step (Reference to section V)

D3 and D5, which may be considered to represent the closest state of the art, relate to HIV integrase inhibitors, which are useful in preventing or treating infections by HIV or for treating AIDS.
Compounds of D3 and D5 merely differ from the subject-matter of present claims 1 and 30 in the absence of a phosphonate group.
The problem to be solved by the present application may therefore be seen in the provision of further derivatives for the inhibition of HIV-integrase.
As cited above, D3 and D5 describe very good HIV integrase inhibitors, which would fall within the meaning of present claims if it were not for the proviso at the end of claims 1 and 30 implying that current compounds must contain at least a phosphonate group.
Nevertheless, the skilled person knows from D6-D8 that phosphorous bearing groups such as phosphonates can be transformed into a prodrug, exhibiting in this way an enhanced penetration through biological membranes (cf. D6 pages 3-5; D7 pages 4109-4110 and D8 pages 498-499).
It is thus believed that the combination of D3/D5 with the teaching of D6-D8 would obviously lead at present compounds.
Moreover, as far as the scope of the claims is concerned, the Applicant's attention is drawn to the fact that only such compounds can be claimed which represent a solution of the problem underlying the application in suit. The extent of a reasonable generalisation depends on the credibility that substantially all the alternatives claimed must be a solution to the problem. Extremely broad generalisations like "substituted", "alkyl", "aryl", "protecting group" etc. (cf. for instance claims 1, 17, 30 and 45) are in contradiction with the basis of qualitative structure-activity-relationships. Taking into account the relevant state of the art and the common knowledge, it appears not to be predictable that all alternatives claimed would achieve the same technical effect.

Consequently, the subject-matter of claims 1-65 does not meet the criteria of Article 33(3) PCT.

5) Industrial applicability (Reference to section V)

For the assessment of the present claims 64-65 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the

use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6) Further observations (Reference to section VIII)

6.1) Prodrug: protection cannot be sought for speculative compounds, which have yet to be prepared and investigated. Although there is an indication within the application as to what it may be, a prodrug is not a definable term as regards its structure. The skilled person has no indication as to what falls within this definition, and it should thus be deleted. No analysis of novelty and inventive step has therefore been made for all the compounds which are combinations of "prodrug" and of derivatives of claims 1 and 30.

6.2) It is not clear what is meant under "certain compounds of tables 1-5" as written on pages 152-153, as these tables have not been found in the application.

6.3) Claim 30 should be dependent on claim 1 (Rule 6.4 PCT).